Managing Acute Uncomplicated Cystitis in Women in the Era of Antibiotic Resistance: A Case-Based Approach

The first in a series of educational newsletters

PRESENTED BY

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- Topical estrogen therapies for the prevention of urinary tract infection
- All urinary tract infection therapies mentioned for prophylaxis

TARGET AUDIENCE

Urologists, obstetricians/gynecologists, primary care physicians (general practitioners, family practitioners, internal medicine physicians) and other healthcare professionals who care for patients with acute uncomplicated cystitis.

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MANAGING ACUTE UNCOMPLICATED CYSTITIS IN WOMEN IN THE ERA OF ANTIBIOTIC RESISTANCE: A CASE-BASED APPROACH

INTRODUCTION

This is the first in a series of newsletters based, in part, on presentations from an August 2002 roundtable presented by The Office on Women's Health of the U.S. Department of Health and Human Services and jointly sponsored by the University of Washington School of Medicine and IMED Communications entitled *Managing Acute Uncomplicated Cystitis in Women in the Era of Antibiotic Resistance*. The goal of the roundtable was to examine the impact of antibiotic resistance on the management of acute uncomplicated cystitis (AUC), or urinary tract infection (UTI), in women. This first newsletter examines the diagnosis and management of AUC in healthy, adult women of all ages.

AUC is a symptomatic infection of the bladder, or lower urinary tract, that occurs in a patient with a normal genitourinary tract.[1-3] Diagnosis is usually based on a clinical presentation that includes 1 or more of the following: dysuria, urinary frequency/urgency, voiding small volumes, incontinence, hematuria, and suprapubic or low back pain. Laboratory findings include bacteria in bladder urine, usually with pyuria and frequently hematuria (Table 1).[1,3-5] Routine urinalysis or urine culture is not generally recommended. Treatment of cystitis in healthy women traditionally uses empiric antibiotic therapy of 3 or 7 days (Table 2, page 2).[6-13] Long-term medical sequelae of AUC in otherwise healthy adults are rare,[5,14] although the short-term morbidity and disability from AUC can be significant.[15] In contrast, UTIs occurring in pediatric patients; patients with comorbidities including diabetes, renal failure, or pregnancy; or patients with functional, metabolic/immunologic, or structural abnormalities are often considered to be "complicated" infections that require pretherapy urine culture and longer-duration treatment courses and may be associated with significant morbidity.[16]

AUC has predictable bacteriology (Table 1). The overwhelming majority of AUC cases are caused by *Escherichia coli* (80%-90%) or *Staphylococcus saprophyticus* (5%-15%); other, less common uropathogens include *Klebsiella pneumoniae*, *Proteus* spp, and *Enterococcus* spp (5%-10%).[17-20] This predictable bacteriology, coupled with known susceptibility, supports the recommendation of 3-day therapy with trimethoprim/sulfamethoxazole (TMP/SMX) as empiric antibiotic treatment.[6] TMP/SMX has been in use for several decades and is considered first-line therapy for AUC. The recommended regimen is 160 mg TMP/800 mg SMX BID for 3 days or in patients with sulfa allergies, 200 mg TMP BID. Clinical cure rates of up to 90% have been reported with this agent.[7] However, increases in resistance rates of *E coli* to TMP/SMX have challenged the empiric use of this agent.[17,21] In geographic regions where TMP/SMX resistance is a concern (i.e., >10%-20%), alternative agents such as fluoroquinolones, nitrofurantoin, or fosfomycin are recommended.[6,22]

LEARNING OBJECTIVES

After completion of this program, the participant should be able to:

- Discuss the etiology of acute cystitis
- Describe the consequence of the increase in antimicrobial resistance on the management of acute cystitis in the general population and the older woman
- Determine the risk factors that influence the development and recurrence of acute cystitis throughout a woman's lifetime
- Identify the benefits and disadvantages of both traditional and newer antimicrobial agents
- Review the latest pharmacologic/nonpharmacologic strategies for prevention
- Explain the impact of age on management strategies for women with acute cystitis

TABLE 1
ACUTE UNCOMPLICATED CYSTITIS (AUC)

Diagnosis/clinical presentation

- Dysuria, frequency/urgency, hematuria
- Voiding small volumes
- Incontinence
- Suprapubic/low-back/abdominal pain
- Patient history of AUC

Predictable bacteriology

- *Escherichia coli* (80%-90%)
- *Staphylococcus saprophyticus* (5%-15%)
- *Klebsiella pneumoniae*, *Proteus* spp, *Enterococcus* spp (5%-10%)

Medical sequelae

- No known long-term sequelae
- Significant short-term morbidity
- Recurrence is common

TABLE 2

COMMONLY USED ANTIMICROBIAL AGENTS FOR ACUTE UNCOMPLICATED CYSTITIS

Drug	Regimen	Clinical Response/ Resolution*	Bacteriologic Response*	Mechanism of Action (MOA)**	Resistance Among *E coli*
TMP/SMX	160 mg TMP/ 800 mg SMX BID X 3 d	90%[7]	94%-96%[7]	TMP blocks tetrahydrofolic acid production; SMX inhibits bacterial synthesis of dihydrofolic acid	↑↑
Nitrofurantoin monohydrate/macrocrystals	100 mg BID X 7 d	89%-94%[8]	78%-79%[8]	Inhibits protein synthesis, aerobic energy metabolism, DNA/RNA synthesis, and cell wall synthesis	–
Nitrofurantoin macrocrystals	50 mg QID X 7 d	90%-92[8]	72%-76%[8]	Inhibits protein synthesis, aerobic energy metabolism, DNA/RNA synthesis, and cell wall synthesis	–
Fosfomycin tromethamine	3-g sachet (single-dose therapy)	82%[9]	70%[9]	Inactivates enzyme enolpyruvyl transferase; Interferes with DNA gyrase	↑↑
Ciprofloxacin	100 mg BID X 3 d	87%-95%[10]	91%-97%[10]	Interferes with DNA gyrase	↑
	250 mg BID X 3 d	94%[11]	90%[11]		
	250 mg BID X 7 d	94%[10]	97%[10]		
Levofloxacin	250 mg q24h X 3 d	98%[12]	96%[12]	Inhibits topoisomerase IV and DNA gyrase	?
Gatifloxacin	200 mg q24h X 3 d	Not reported[13]	95%[13]	Inhibits topoisomerase IV and DNA gyrase	?

*Responses measured varied per study from 1 to 14 days posttherapy.

**MOA based on drug package inserts.

SDT = single-dose therapy.

Fluoroquinolones are broad-spectrum agents commonly used in the treatment of respiratory tract infection, skin and soft tissue infections, and UTI. There are 7 fluoroquinolones with Food and Drug Administration indications for UTI. Ciprofloxacin, gatifloxacin, levofloxacin, and norfloxacin are commonly used, and enoxacin, lomefloxacin, and ofloxacin are rarely used. Of the available alternatives to TMP/SMX, fluoroquinolones achieve higher bacteriologic cure rates and their efficacy against most *E coli* has led to recommendations for their empiric use in the management of AUC where resistance to TMP/SMX is greater than 10%-20%.[6] However, many clinicians believe this important class of agents should be reserved for the management of more serious infections.[23] Serious adverse reactions with the fluoroquinolones are rare;[24,25] the most commonly reported adverse events include gastrointestinal and central nervous system effects and phototoxicity which are usually mild-to-moderate and are reversible.[24,26-29] Fluoroquinolones may interact with some medications including warfarin, cyclosporine A, theophylline, and caffeine.[26,29-31] In addition, national and international data indicate increasing rates of resistance to fluoroquinolones.[32-36] In one recent study based on data from The Surveillance Network Database-USA, in which more than 286,187 isolates were analyzed to determine trends in the activities of TMP/SMX, ampicillin, ciprofloxacin, and nitrofurantoin, ciprofloxacin was the only agent studied to demonstrate a consistent stepwise increase in resistance from 1995 (0.7%) to 2001 (2.5%).[37] Clinicians now must weigh the high efficacy of the fluoroquinolones against the potential for increasing resistance. Widespread empiric use of fluoroquinolones in the management of AUC in otherwise healthy women might further contribute to fluoroquinolone resistance and ultimately compromise their efficacy for more serious infections.[17,38,39]

Nitrofurantoin is an agent that has remained effective for nearly 50 years in the treatment of acute cystitis. Clinical cure with a 7-day regimen remains high (94%),[8] and, unlike with other antimicrobials, resistance rates among uropathogenic *E coli* have remained low (<2%). The failure of resistance to emerge despite prolonged use may be, in part, attributed to multiple mechanisms and sites of action.[22,40] Nitrofurantoin is a urospecific agent limited to the management of acute cystitis for uropathogens. It is also active against most strains of vancomycin-resistant enterococci.[22] Activity against some other gram-negative rods, that occasionally cause AUC, e.g., *Proteus mirabilis*, is less than with *E coli*. Nitrofurantoin is also a first-line choice for prophylaxis of recurrent acute, uncomplicated urinary infection and prolonged use has been shown to be safe with low rates of resistance.[41] Nausea and headache are the most frequently reported adverse effects.[8] Nitrofurantoin is associated with acute interstitial pneumonitis which occurs rarely and resolves with rapid withdrawal of the drug and supportive care.[42]

Fosfomycin tromethamine single-dose therapy (SDT) is a relatively recent addition to the UTI armamentarium in North America. There are limited published clinical trials describing the efficacy or safety of fosfomycin SDT. Some studies suggest lower efficacy for cystitis than with TMP/SMX or fluoroquinolones.[6,42] In one study, fosfomycin SDT appeared to be comparable in efficacy to nitrofurantoin 7-day therapy.[43] However, fosfomycin is not recommended for use in complicated infections or for prophylaxis because of the rapid emergence of resistance.[16] The most frequently reported AE is diarrhea (10.4%); more serious adverse events have rarely been reported but include angioedema and aplastic anemia.[9]

The 4 cases presented in this newsletter highlight the challenges facing clinicians who diagnose and manage AUC in healthy women. The cases within this newsletter include:

- A sexually active 20-year-old college student living in Colorado. Does she have a UTI or a sexually transmitted infection (STI)? Does her sexual activity or contraceptive method contribute to her recurrent infections? Is she a candidate for self-treatment or prophylaxis? Do the local geographic resistance rates affect antibiotic selection?
- A 35-year-old international flight attendant based in New York with recurrent cystitis. What are the general guidelines for management of AUC? Does her travel abroad increase the risk of unusual or resistant organisms? Does she require prophylaxis?
- A 55-year-old postmenopausal woman. How do treatment approaches differ for this age group? What effect does lack of estrogen have on incidence, diagnosis, presentation, or management of AUC? Because women of this age have an increased risk of comorbid conditions, does this have any effect on UTI management?
- A 78-year-old postmenopausal woman with incontinence. Is she living on her own or in a long-term care facility? Is this long-term asymptomatic bacteriuria (ASB) or symptomatic cystitis? Is there an underlying bladder or urinary tract abnormality? What is the impact of multidrug resistance in elderly patients? Are there other possible comorbidities present, such as diabetes? Is there any effect on presentation, diagnosis, and management?

CASE 1: UTI VERSUS STI

This case describes a young, sexually active woman with a history of UTI. Diagnosis should rule out an STI, and current/future management must take into consideration her past history, contraceptive practices, and sexual activities. Empiric management should also consider local geographic resistance patterns.

Clinical Presentation and History

A 20-year-old student living in Denver, Colorado, presented to the university health center with acute onset dysuria and increased urinary frequency. She had no fever, nausea, or vomiting; there was no complaint or evidence of vaginal discharge or odor, and no lower abdominal pain on physical examination. Dipstick urinalysis showed pyuria and hematuria. The student is sexually active, but not in a committed relationship and uses a diaphragm with spermicide for contraception. She has no known medical concerns and no known allergies, is not receiving medication for any illness, and is in good overall health. She has been treated twice for UTIs during the 2 years since she first became sexually active.

Diagnostic Considerations

In this case, a differential diagnosis for acute cystitis, urethritis from an STI, and vaginitis should be considered based on the symptomology of acute dysuria (Table 3).[1,3-5,19,44] This patient presented with a combination of additional signs and symptoms, including pyuria, hematuria, and frequency that, when taken together, are strongly suggestive of cystitis.[1] The absence of vaginal discharge or irritation further increases the probability of cystitis rather than urethritis or vaginitis.[1] The absence of nausea, vomiting, or abdominal pain makes the diagnosis of acute pyelonephritis or pelvic inflammatory disease unlikely.

This patient's young age, sexual activity, and contraceptive choices also contribute to a diagnosis of cystitis. Epidemiologic studies indicate that women 18-24 years of age have the greatest incidence of UTI.[45] In addition, research has demonstrated that a new sexual partner; recent sexual intercourse; or the use of spermicides, a diaphragm, and/or spermicide-coated condoms increases the risk of UTI.[5,15,45-48] Recent intercourse, spermicide use, or a new sexual partner also increases the risk of recurrent UTI.[49] Finally, a history of prior UTI increases the risk of future UTI,[3,45] and women with recurrent UTI (RUTI) are accurate in self-diagnosis for current UTI.[50,51]

In summary, this patient's set of clinical symptoms, past history of UTI, and current sexual and contraceptive practices led to a diagnosis of acute cystitis. With this presentation, no additional diagnostic tests are indicated. If the history and physical examination are inconclusive for UTI, a urine dipstick and, possibly, culture would be necessary to make a UTI diagnosis.[1]

Management Considerations

Empiric Management

As the most probable etiology of this patient's UTI is *E coli*, empiric antimicrobial selection should include agents with good activity against *E coli*. The Infectious Diseases Society of America (IDSA) published evidence-based guidelines for the antimicrobial treatment of AUC in women (Table 4, page 4).[6] The guidelines recommend 3-day therapy regimens for healthy, nonpregnant women.[6,52] The IDSA guidelines determined that TMP/SMX or TMP for 3 days is the current standard of therapy for AUC; however, in communities with a high rate of TMP/SMX resistance (>10%-20%), the IDSA recommends the use of a fluoroquinolone for 3 days, nitrofurantoin (for example, monohydrate/macrocrystals 100 mg BID) for 7 days, or SDT fosfomycin tromethamine.[6,18] Beta-lactam agents are not recommended. The high rate of resistance to amoxicillin, estimated at up to 33% in the United States, limits its use as empiric therapy for AUC.[21,53]

TABLE 3

DIAGNOSING ACUTE DYSURIA IN WOMEN

Diagnosis	Pyuria	Hematuria	Pathogen	Symptoms/Signs/Factors
Cystitis	Usually	Sometimes	*E coli*, *S saprophyticus*, *Proteus* spp, *Klebsiella* spp	Abrupt onset, severe symptoms: dysuria,frequency/urgency, suprapubic/low-back pain or tenderness
Urethritis	Usually	Rarely	*Chlamydia trachomatis*, *Neisseria gonorrhoeae*, herpes simplex virus	Gradual onset, mild symptoms: vaginal discharge/bleeding, new sexual partner, abdominal pain, external lesions
Vaginitis	Rarely	Rarely	*Candida* spp, *Trichomonas vaginalis*	Vaginal discharge/odor, pruritus, dyspareunia, vulvovaginitis on exam, external dysuria

Adapted with permission from Stamm WE, Hooton TM. *N Engl J Med.* 1993;329:1328-1334.[19]

TABLE 4

IDSA PRACTICE GUIDELINES: ACUTE UNCOMPLICATED CYSTITIS

Duration of treatment

- Single-dose therapies less effective than 3-day regimens
- 3-day regimens equivalent to 7 to 10-day therapies for TMP, TMP/SMX, and fluoroquinolones

Empiric therapy

- TMP/SMX or TMP alone
- If known resistance >10% to 20%; alternative agents
  - Fluoroquinolone X 3 days
  - Nitrofurantoin X 7 days
  - Fosfomycin SDT

Source: Warren JW, et al. *Clin Infect Dis.* 1999;29:745-758.[6]

Role of Antibiotic Resistance

Empiric therapy with TMP/SMX could be an appropriate selection, especially if she has not been treated with TMP/SMX.[35] However, this patient resides in Denver, Colorado, and the demonstrated rate of *E coli* to TMP/SMX resistance in the Mountain region of the United States is high (20%) (Figure 1).[54] In light of this, TMP/SMX may not be appropriate as a first-line agent; TMP/SMX therapy will fail for up to 50% of women if they have TMP/SMX-resistant organisms.[55,56] Because TMP/SMX resistance is a concern, fluoroquinolones for 3 days or nitrofurantoin for 7 days could be considered for therapy.

Special Considerations

Among premenopausal women, UTI prevention should consider sexual intercourse and spermicide exposure. The use of a diaphragm/spermicide increases this patient's risk of UTI, and alternate forms of contraception were discussed with the patient. Condom use was strongly advised. This patient replaced the diaphragm/spermicide with an oral contraceptive (OC) and will use condoms to prevent STIs. Voiding soon after coitus may reduce the risk of UTI.[57]

This patient has had 3 diagnosed UTIs in 2 years. Antimicrobial prophylaxis is generally indicated for women who experience 3 or more UTIs within a 1-year period[48] or 2 infections within a 6-month period.[58] Both continuous and postcoital antimicrobial prophylaxis strategies are highly effective in reducing UTI risk. Before instituting a prophylactic regimen, the clinician should discuss with the patient whether she is bothered by her UTIs and the frequency of their recurrence. Although there is no evidence that recurrent AUC has any long-term medical sequelae, the short-term morbidity can be significant. In college women, an episode of AUC can lead on average to 6.1 symptomatic days, 2.4 days of restricted activity, and 0.4 days of bed rest.[15] As this patient was not overly bothered by the infections and was experiencing a relatively low frequency, prophylactic antimicrobial therapy would not be suggested. The patient was counseled on instituting basic behavioral changes around her sexual activities (e.g., voiding after intercourse).

Case Conclusion and Commentary

This 20-year-old patient presented with a classic clinical presentation of acute cystitis—acute dysuria, pyuria, hematuria, and urinary frequency, as well as a history of prior UTIs. Her general good health, young age, sexual activity, and contraceptive practices strongly contributed to the diagnosis of acute cystitis. Laboratory testing to confirm the diagnosis was not necessary. Management focused on 3 components: antimicrobial therapy for the current infection, suggested behavioral alterations to minimize recurrences, and discussions for management of subsequent recurrences including prophylaxis. The high rate of *E coli* resistance to TMP/SMX (20%) in the Mountain region of the United States (Figure 1) was an important factor in antimicrobial selection. Nitrofurantoin for 7 days or a fluoroquinolone for 3 days provide appropriate alternatives in light of the resistance data. The patient opted to switch her contraceptive choice from the diaphragm with spermicidal agent to an OC with condoms. Self-start management was not suggested, given the low frequency of recurrence.

CASE 2: RUTI AND PROPHYLAXIS

This case describes a 35-year-old international flight attendant based in New York who presented with RUTIs. The clinical presentation strongly suggested a diagnosis of AUC. Is a telephone-based consultation sufficient for diagnosis? Consideration must be given to the risk of unusual or resistant organisms because of her international travel.

Clinical Presentation and History

A 35-year-old married mother of 2 telephoned her family physician with complaints of dysuria, urinary frequency, voiding small volumes, and slight lower back pain. She reported no fever, nausea, or vomiting, no vaginal discharge or odor, and no abdominal pain. She had been treated with TMP/SMX for 3 UTIs in the past 14 months. She is monogamous and uses OCs. Her currently assigned flight route was between New York and Western Europe.

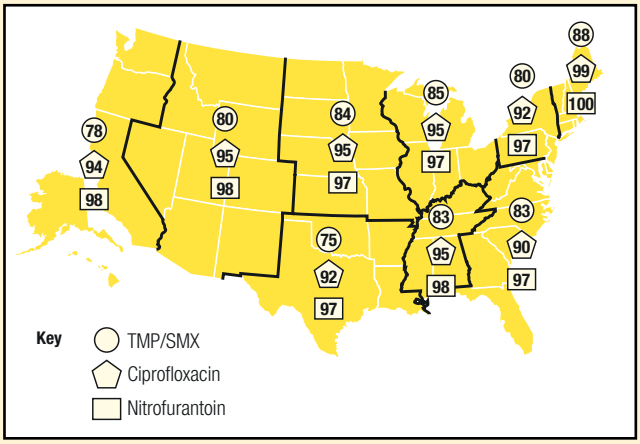
Diagnostic Considerations

The diagnosis appeared straightforward with this patient. She described classic symptoms of AUC with no complicating illnesses. Her personal history made urethritis from an STI unlikely, and the absence of vaginal discharge or odor ruled out vaginitis. Furthermore, her strong history of prior UTI suggests that RUTIs are highly likely and *E coli* is the likely cause of her infection.

There is a wide variety of strategies used by family physicians for the management of cystitis.[59] Recent guidelines suggest that telephone

FIGURE 1

GEOGRAPHIC VARIATION IN ANTIMICROBIAL *E COLI* SUSCEPTIBILITY: 2002*



*Susceptibility rates of urinary *Escherichia coli* isolated in hospital laboratories from ambulatory and outpatient men and women 15-50 years of age.

Source: TSN® Database-USA. Copyright© 2002;Focus Technologies, Inc.[54]

management of AUC is effective and safe.[60-62] Diagnosis of AUC in low-risk women is predominantly based on the presence of specific symptoms (dysuria, frequency, hematuria) and the absence of other symptoms (vaginal discharge, odor, irritation). Physical examination is often only marginally useful in establishing a diagnosis of cystitis, and urine culture or laboratory analysis is reserved for complicated infections or for women whose diagnosis is not clear. Whereas telephone management without confirmatory positive urine cultures potentially results in the unnecessary use of antibiotics in some women, a telephone-based diagnostic approach appears to be appropriate and reasonable in many clinical settings. In addition, accuracy of self-diagnosis among women with RUTI appears to be very high.[1]

Management Considerations

Empiric Management

According to the IDSA guidelines, empiric antimicrobial selection for AUC would be standard 3-day therapy with TMP/SMX; alternatives would include a fluoroquinolone, nitrofurantoin, or fosfomycin. This patient had recently used TMP/SMX, increasing the possibility that the UTI is caused by a TMP/SMX-resistant uropathogen (Table 5).[36,63] In addition, she lives in New York, a region with a high rate of resistance to TMP/SMX (20%) (Figure 1), and travels frequently to Spain where the resistance to fluoroquinolones is high (20%).[17,32]

Role of Antibiotic Resistance

Susceptibility rates of urinary *E coli* isolates to TMP/SMX in the Mid-Atlantic region of the United States where New York is located (Figure 1) are low at 80%, suggesting empiric therapy with an alternative antimicrobial therapy should be considered. Research has shown a lower clinical response rate to TMP/SMX at 1-4 weeks among TMP/SMX-resistant infections.[55,56] In addition, the susceptibility rate of urinary *E coli* to ciprofloxacin in this region of the United States is 92%,[54] and increasing rates of resistance to fluoroquinolone agents elsewhere raise concerns about widespread empiric use of this agent. Since *E coli* susceptibility to nitrofurantoin, both in the Mid-Atlantic region (97%)[54] and in Europe (93%-94%),[51] remains high, she was started on a 7-day regimen of nitrofurantoin macrocrystals followed by low-dose nitrofurantoin prophylaxis.

Special Considerations: UTI Prophylaxis

This patient's history of frequent RUTIs led to discussion regarding prophylaxis. Antimicrobial management of RUTI may include continuous low-dose antimicrobial therapy, postcoital SDT, or self-start regimens. Continuous low-dose prophylaxis is frequently initiated for 6 months and may be reinitiated if recurrence occurs after it is discontinued. Women with RUTI can accurately self-diagnose without laboratory testing,[51] and self-initiated therapy is safe and effective in this group.[64] Agents used effectively for long-term continuous UTI prophylaxis include nitrofurantoin (50 mg/day), TMP alone (100 mg/day) or with SMX (40/200 mg daily or 3 times per week),[65] or the fluoroquinolones, norfloxacin (200 mg 3X/week) and ciprofloxacin (125 mg/day).[48,66] Postcoital prophylaxis should be considered if her UTIs were temporally associated with sexual intercourse. Postcoital prophylaxis is effective with single-dose administration of any of the above agents, as well as cephalexin (250 mg), ofloxacin (100 mg), and ciprofloxacin (250 mg).[2,67] Self-diagnosis and self-start therapy using short-course durations of appropriate antimicrobials has also been shown to be safe, effective, and economical for patients with a history of RUTI.[68] Women with strong patient–clinician relationships, who are adherent to medication regimens, and who do not use spermicides for birth control may be most likely to respond well to this option.[50,68] Fosfomycin is not recommended for prophylaxis because of the high risk of resistance with extended use.[16]

TABLE 5

HOST RISK FACTORS FOR UTI CAUSED BY TMP/SMX-RESISTANT *E COLI*

	Odds Ratio (95% Confidence Interval)	
	Wright	**Brown**
Recent hospitalization	3.1 (1.2, 8.4)	ND
Diabetes	2.5 (1.1, 5.7)	ND
Use of any antibiotic	4.5 (2.0, 10.2)	2.4 (1.1, 5)
Use of TMP/SMX	5.1 (2.2, 11.5)	16.7 (3, 97)

ND = no data.

Sources: Wright SW, et al. *J Gen Intern Med.* 1999;14:608-609,[63] Brown PD, et al. *Clin Infect Dis.* 2002;34:1061-1066.[36]

The type of travel this patient's job entailed necessitated that she remain hydrated, and she frequently drank cranberry juice, based on anecdotal suggestions that it prevents UTIs.[14,22] Although the current clinical evidence remains inconclusive, recent studies suggest a beneficial effect.[46,69,70] Cranberries, lingonberries, and blueberries contain condensed tannins called proanthocyanidins that can prevent the attachment of P-fimbriaed *E coli* to uroepithelial cells. The benefit of cranberry products requires further evaluation and comparison to antimicrobial prophylaxis.

Case Conclusion and Commentary

This patient had a classic symptomatic presentation suggestive of acute uncomplicated UTI. Postcoital urination was suggested and prophylaxis should be offered. Empiric management with TMP/SMX was not recommended based on a high rate of TMP/SMX resistance in her geographic location and recent therapy. As a result, acute and prophylactic treatment with nitrofurantoin was recommended. In addition, the clinician did not discourage her from drinking cranberry juice as a further preventive measure but cautioned her regarding the sugar/calorie intake.

CASE 3: UTI IN A POSTMENOPAUSAL WOMAN

In this case, a healthy, active, and independent postmenopausal woman in Oregon presented to her gynecologist with acute cystitis. The diagnosis and management of her UTI must consider estrogen deficiency.

Clinical Presentation and History

A 55-year-old married woman contacted her gynecologist with complaints of dysuria, urgency, and frequency. She had mild suprapubic tenderness, no fever or chills, and no vaginal discharge. Her last menstrual period had been 3 years earlier, and she was not receiving hormone replacement therapy (HRT). She had had a cluster of RUTIs during her childbearing years but had not had a UTI for more than 20 years. Upon questioning, she reported a recent history of vaginal irritation, particularly associated with sexual intercourse. Her vital signs were all within the normal range.

Diagnostic Considerations

In this case, the clinical presentation strongly suggests acute cystitis. Suprapubic tenderness is not a common finding but it is fairly specific for cystitis.[3] The report of vaginal irritation with intercourse suggests a postmenopausal estrogen deficiency rather than vaginitis. Although there is an increase in the prevalence of asymptomatic bacteriuria (ASB) with age, which does not require antimicrobial therapy, this patient's

presentation was symptomatic. Her history of premenopausal UTI means she is at increased risk of postmenopausal UTI.[71] Finally, a deficiency of vaginal estrogen may be a risk factor for postmenopausal UTI.[72]

Management Considerations

Empiric Management

Management should focus on antimicrobial therapy for the current UTI and consideration of topical estrogen vaginal cream. Diagnosis (including etiology) and empiric management of AUC in this postmenopausal patient are similar to those for a pre- or perimenopausal patient. As with a younger woman, the etiology is most likely to be *E coli*.[73] Empiric therapy would indicate 3-day treatment with TMP or TMP/SMX, excluding other confounding factors such as antibiotic resistance.

Role of Antibiotic Resistance

Susceptibility of urinary *E coli* to TMP/SMX in Oregon is low (78%) (Figure 1), so alternative treatment should be considered (Table 6).[54] In comparison, *E coli* susceptibility to either fluoroquinolones (94%) or nitrofurantoin (98%) remains high in the Northwestern United States. Either of these options would be appropriate.

Special Considerations: Postmenopausal Estrogen

Management must take into consideration the changes in her vaginal flora associated with an absence of estrogen. Enterobacteriaceae, especially *E coli*, replace lactobacilli as the predominant colonizers of the vagina in postmenopausal women with RUTI.[74] In such women, topical estriol has been shown to reconstitute the vaginal flora with lactobacilli, reduce vaginal colonization with *E coli*, and prevent UTIs;[74] conflicting results have been obtained using an estradiol-releasing vaginal ring.[56,75]

There is currently no evidence of harmful systemic effects (such as cardiovascular effects) associated with topical hormonal therapies, including the intravaginal administration of estrogen to postmenopausal women.[74]

Case Conclusion and Commentary

In healthy, independent postmenopausal women, acute cystitis can be diagnosed and managed similarly to AUC in younger, premenopausal women. However, the lack of estrogen associated with menopause may contribute to the risk of UTI, and many postmenopausal women, including this patient, may benefit from topical estrogen treatment to prevent future UTIs. Topical estrogen therapy will also alleviate this patient's complaint of vaginal irritation. An important consideration is the risk of comorbidities. Diabetes, prior genitourinary surgery, and cystoceles are more common among postmenopausal women and can influence the diagnosis and management of UTI.

CASE 4: GERIATRIC COMPLICATIONS OF UTI

An elderly woman was brought to her primary care physician with complaints of frequent urination and incontinence. Is it asymptomatic bacteriuria (ASB) or a UTI? Does the incontinence indicate an underlying bladder or urinary tract abnormality? The increased risk of multidrug resistance (MDR), atypical uropathogens, and comorbidities in the geriatric population must be considered.

Clinical Presentation and History

A 78-year-old woman living in a long-term care facility in Florida is brought to her primary care clinician for management of what appears to be urge incontinence. The patient is alert and afebrile and admits to acute symptoms of dysuria, urgency, frequency, and incontinence. There is no prior history of UTI. She is postmenopausal (last menstrual period at 51 years of age), does not take HRT, and is not currently sexually active. Physical examination and vital signs are normal. She has visible signs of osteoporosis and uses a walker. She is currently receiving multiple medications including an antihypertensive agent, cholesterol-lowering agent, arthritis medication, and a medication for osteoporosis.

Diagnostic Considerations

UTI is the most frequent bacterial infection among patients in long-term care facilities.[76] The majority of these infections are asymptomatic[76] and do not benefit from antimicrobial therapy.[77,78] Diagnosis of symptomatic infection in the elderly institutionalized patient is often problematic and challenging, as a positive urine culture and pyuria do not confirm symptomatic infection.[78] A negative urine culture will generally rule out UTI.[72] Although diagnosis and management of UTIs in healthy, younger postmenopausal women (≤65 years of age) are similar to those in premenopausal patients, there are specific considerations for women >65 years of age. This patient's advanced age increases the likelihood of urologic abnormalities, increased risk of drug-drug and disease-disease interactions, and comorbidities. Because she is a resident of a long-term care facility, she is more likely to have a resistant infection or an MDR infection.[79]

In this population, urine culture and susceptibility testing are necessary before antimicrobial therapy is initiated.[79] ASB is very common in this population.[72,80,81] However, this patient described new and acute symptoms suggestive of lower UTI, i.e., acute cystitis; the absence of additional symptoms suggests the absence of upper-tract infection.[78] She presented with what appeared to be urge incontinence, a common complaint among elderly patients. If incontinence persisted after treatment of the infection, investigation of voiding function should be considered. A cystocele or increased postvoid residual is more common in elderly women and would increase her risk of UTI.[82] She did not have any current or recent catheterization, and there was no history or evidence of neurologic disorders. She also had no known reproductive surgeries. The primary care physician ordered a urine culture, and *Klebsiella pneumoniae* was isolated. The positive culture and symptomatic presentation were consistent with a diagnosis of acute cystitis.

Management Considerations

Empiric Management

ASB is very common in the elderly and rarely necessitates antimicrobial therapy.[83] In contrast, symptomatic infection does warrant treatment, predominantly for symptom relief.[73] UTI in elderly patients is often treated as a complicated infection, since comorbid conditions often exist. Clinicians therefore recommend more conservative approaches for acute cystitis in institutionalized elderly patients, with longer treatment durations (7-10 days for women)[48,73] and using agents that cover a broad spectrum of typical and atypical uropathogens. Treatment selection must also be based on the possibility of drug-drug interactions. Empiric treatment with a fluoroquinolone for 7 days is the first-line choice.[32] Therapy occasionally must be tailored based on the urine culture results. Of the 7 fluoroquinolone agents with indications for UTI, norfloxacin, ciprofloxacin, gatifloxacin, and levofloxacin are the most widely used, whereas enoxacin, lomefloxacin, and ofloxacin are less commonly used. Recent safety concerns about effects of gatifloxacin on blood glucose may limit its use, particularly in elderly and/or diabetic patients. Ciprofloxacin is a possibility, although it inhibits the hepatic cytochrome-P450 enzyme system[29] and this patient is taking multiple medications. Ultimately, the clinician prescribed levofloxacin.

TABLE 6

UNITED STATES SUSCEPTIBILITY DATA: 1ST QUARTER 2002*

	Percent Susceptibility			
	TMP/SMX	**Nitrofurantoin**	**Ciprofloxacin**	**Levofloxacin**
E coli	81	98	93	93
Enterococcus spp	NR	97	55	59
K pneumoniae	90	55	94	95
Proteus mirabilis	82	2	81	82
S saprophyticus	97	99	100	100

TSN® Database, MRL Pharmaceutical Services. Available at: http://www.medscape.com/pages/editorial/resourcecenters/public/uti/rc-uti.ov.[54]

*Susceptibility rates of urinary isolates from hospital laboratories from ambulatory and outpatient men and women 15-50 years of age.

NR = not reported.

Special Considerations

Multidrug Resistance

Several studies have reported 3 independent exposures associated with isolation of an MDR organism from a person with UTI: age >65 years, urinary catheter use, and antibiotic use.[32,35,84] Elderly patients who reside in long-term care facilities are likely to receive repeated courses of antimicrobials and to be exposed to other individuals who are frequently treated with antibiotics. This predisposes institutionalized patients to resistant strains. One definition of MDR has been ampicillin, TMP/SMX, and cephalothin, with or without ciprofloxacin resistance.[84] Some MDR pathogens remain susceptible to nitrofurantoin. However, nitrofurantoin would be appropriate if the causative uropathogen was shown to be susceptible and if there were no signs or symptoms suggestive of upper tract infection.

Comorbidities

Diabetes mellitus is common among elderly patients and may predispose them to UTIs.[14,85] UTIs in patients with diabetes are typically considered to be "complicated" infections, and in one report, diabetes was an independent risk factor for TMP/SMX-resistant pathogens as well as for MDR uropathogens.[35] In addition, incontinence may be an indication of untreated diabetes in the elderly.

Urologic abnormalities are common among elderly women as a result of childbearing, reproductive surgeries, menopausal changes, or other functional or anatomic changes associated with the aging process or with comorbidities of the elderly. Referral to a urogynecologist may be indicated for management of the underlying abnormality.

Case Conclusion and Commentary

Although the clinical presentation of AUC for this patient was similar to that of other uncomplicated infections, her age and living arrangements put her at elevated risk for TMP/SMX-resistant and/or MDR infections. A longer duration of therapy may be required. In addition, her urine culture showed a *K pneumoniae* resistant to TMP/SMX and nitrofurantoin, so treatment was with a fluoroquinolone. Selection of the most appropriate fluoroquinolone agent focused on the pathogen and the possibility of comorbidities or drug interactions. Ciprofloxacin inhibits the hepatic cytochrome P-450 system, raising concerns about drug-drug interactions in this patient. In addition, recent labeling changes for gatifloxacin describe serious disturbances in glucose homeostasis resulting in significant hypo- and hyperglycemic episodes that are of particular concern with elderly (>75 years) patients. As a result, levofloxacin was prescribed.

Her presentation of incontinence, if it persisted after treatment, also warranted additional testing to rule out any underlying urogynecologic abnormalities. The probability of comorbidities and drug-drug interactions increases with increasing age. UTI in patients with comorbidities such as diabetes or genitourinary abnormalities is considered to be a complicated infection and should not be treated empirically as an uncomplicated infection.

CONCLUSIONS

AUC is extremely common among women. Diagnosis of AUC is generally straightforward, relying on the presence of suggestive symptoms (acute dysuria, urinary frequency/urgency, and hematuria) as well as the absence of other symptoms (most notably, fever/nausea, vaginal discharge, and abdominal pain). The bacterial etiology of acute cystitis is predictable, with *E coli* the most common uropathogen. Increasing rates of antibiotic resistance to current standard therapies have been reported and have resulted in a reevaluation of appropriate empiric treatment.

Management of cystitis must balance efficacy and safety with any complicating illnesses or comorbidities and also consider the local resistance data. Clinicians may refer to their local hospitals for susceptibility data, or regional data can be found at http://www.medscape.com/pages/editorial/resourcecenters/public/uti/rc-uti.ov. It is important to recognize that susceptibility data may overestimate the prevalence of drug resistance, especially so since the frequency of urine cultures has dropped. Thus, often only those persons who are suspected of having a resistant uropathogen will be cultured. TMP/SMX (3-day therapy) remains the standard empiric treatment for AUC if the known resistance rates in the geographic region in question are low (<20%). However, IDSA guidelines recommend the empiric use of a fluoroquinolone (3 days), nitrofurantoin (7 days), or fosfomycin (SDT) in areas of high antibiotic resistance.[6] These alternative regimens should be considered for patients with risk factors for TMP/SMX-resistant infections. Use of fluoroquinolones for the empiric management of acute uncomplicated cystitis remains controversial, and trends towards increasing *E coli* resistance in all urinary tract isolates have approached 10% in some regions of the United States.[54] Clinicians may consider reserving these broad-spectrum agents for more severe infections to minimize the risk of increasing fluoroquinolone resistance. Fosfomycin is a recent addition to the UTI armamentarium, and there is limited clinical experience in North America with fosfomycin SDT. Nitrofurantoin 7-day therapy has been available for almost 50 years and achieves clinical cure rates of 80% to 94%, and susceptibility continues to remain high to *E coli* in all geographic regions.

Clinicians must also consider the need for behavioral interventions, pharmacologic or nonpharmacologic prophylaxis, and reevaluation of contraceptive options. Topical estrogen cream may be indicated for postmenopausal women. Whenever possible, underlying urogynecologic abnormalities should be addressed to reduce the risk of recurrent infections.

In summary, acute uncomplicated UTI is a common problem affecting a majority of women at least once in their lives. Increasing rates of antibiotic resistance have challenged traditional empiric therapy of TMP/SMX; now concerns have arisen regarding the emergence of fluoroquinolone resistance in some areas. The utility of fluoroquinolones for serious infections has led to recommendations limiting their empiric use in the management of uncomplicated, benign infections such as cystitis; alternative agents such as nitrofurantoin and, possibly, fosfomycin should be considered.

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MANAGING ACUTE UNCOMPLICATED CYSTITIS IN WOMEN IN THE ERA OF ANTIBIOTIC RESISTANCE: A CASE-BASED APPROACH

CME Credit Information and Posttest Assessment

Course No. EN0301 **For Primary Care Physicians, Obstetrician/Gynecologists, Urologists, and Healthcare Professionals Who Treat Patients With Acute Cystitis**

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Washington School of Medicine and IMED Communications. The University of Washington School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The University of Washington School of Medicine designates this educational activity for a maximum of 1.0 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

To apply for category 1 credit, you must:

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I certify that I spent ____ hours in this CME activity as indicated by my signature below.

_____

Signature

Within 2 weeks following the receipt of this form, a transcript of your category 1 hour will be mailed to you. Credit hours for this newsletter may be obtained from January 2003 through January 2005.

POSTTEST ASSESSMENT: *Please circle the correct answer.*

1. Urine culture and susceptibility testing are recommended for the diagnosis of UTI:
   a. In all patients presenting with UTI symptoms
   b. In all patients >55 years of age
   c. In all symptomatic patients living in long-term care facilities

2. The triad of signs and symptoms most suggestive of cystitis includes:
   a. Dysuria, bacteriuria, lower back pain
   b. Dysuria, urinary frequency, pyuria
   c. Dysuria, vaginal discharge, pyuria
   d. Pyuria, vaginal odor, suprapubic pain

3. IDSA empiric management guidelines for uncomplicated cystitis recommend as first-line treatment:
   a. Single-dose antimicrobial regimens for healthy nonpregnant women
   b. TMP/SMX if known community resistance <10%-20%
   c. Fluoroquinolones if known community resistance <10%-20%
   d. TMP/SMX if known community resistance >10%-20%

4. Which of the following agents is not currently recommended for UTI prophylaxis?
   a. Nitrofurantoin
   b. Gatifloxacin
   c. TMP/SMX
   d. TMP

5. Which of the following increases a woman's risk of cystitis?
   a. Recent sexual intercourse
   b. Diaphragm/spermicide use
   c. New sexual partner
   d. Prior UTI
   e. All of the above

6. Which of the following nonantimicrobial recommendations has been demonstrated to reduce RUTI in postmenopausal women?
   a. Systemic estrogen therapy
   b. Topical/intravaginal estrogen
   c. Cranberry or lingonberry products
   d. Frequent intercourse

7. The most common uropathogens of AUC are:
   a. *E coli* and *S saprophyticus*
   b. *E coli* and *P mirabilis*
   c. *E coli* and Group B streptococci
   d. *E coli* and *Pseudomonas aeruginosa*

8. Resistance rates of uropathogenic *E coli* to nitrofurantoin for cystitis are currently estimated at:
   a. <2%
   b. 3%-5%
   c. 8%
   d. >10%

9. Antimicrobial prophylaxis may be considered for women with:
   a. One episode of AUC per year for 4 years
   b. Two episodes of AUC per year for 2 years
   c. Three episodes of AUC in a 12-month period
   d. A current episode of AUC and a history of RUTI

10. First-line therapy for treating bacteriuria in an elderly woman living in a long-term care facility with no genitourinary symptoms is:
    a. Ciprofloxacin BID x 7 days
    b. TMP/SMX x 7 days
    c. Levofloxacin QD x 7 days
    d. None of the above

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EVALUATION FORM

We would appreciate your answers to the following questions in order to help us plan for future activities of this type.

1. How would you rate:

(please ✔)	Excellent	Good	Fair	Poor
a. Value of the topic	❑	❑	❑	❑
b. Relevance to your practice	❑	❑	❑	❑
c. Organization of newsletter	❑	❑	❑	❑
d. Publication length	❑	❑	❑	❑
e. Quality of information	❑	❑	❑	❑

2. Were the goals and objectives clearly stated and achieved? ❑ Yes ❑ No

3. Will reading this newsletter change the way in which you manage patients? ❑ Yes ❑ No

   Please be as specific as possible: _____

4. How do you prefer to receive continuing medical education information? (On a scale of 5 to 1, please score each of the following: 5=very useful; 3=somewhat useful; 1=don't use)

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5. In your opinion, was the information in this newsletter biased toward any commercial product or service? ❑ Yes ❑ No

   If yes, please comment: _____

6. Do you believe such materials, supported by educational grants from industry, are: 10 very appropriate/useful, 0 not appropriate/useful? _____

7. Additional comments and/or suggested topics for future CME activities: _____

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